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EDITORIAL

The many mechanisms of action of Chloroquine: to use or not to use (in COVID-19) that is the question

It seems that history repeats itself. Yet again, in the 21st Century, chloroquine (CQ) and hydroxychloroquine (HQ) are involved in deciding the outcome of battles that will change the course of history. But in today's battle against COVID-19, the question is whether chloroquine is a weapon of good or bad. Use of the extract of the bark of the *Cinchona officinalis* to fight fever has been taking place for centuries (originally in Peru) being introduced in Europe in 1663 by the Spanish Conquistadors. Quinine was also instrumental in protecting invaders in their bid for conquest; most notably the English in India and the Dutch in the Indonesian islands. In the American secession war, the Peruvian bark extract was, at that time, exported by sea. The northern coalition that dominated the sea during the war blocked the supply to the South. It has been estimated that for every three soldiers killed in battle another five were killed by malaria. Clearly this medicinal product played a major part in the outcome of this American war. Today, again history repeats, and yet again this drug is likely to play a major part in determining the politics of the USA.

In the 19th century, there was considerable interest from the chemical industry to isolate the active principle of the bark extract and define its structure; and it was in 1820 that quinine was first isolated with chloroquine discovered in 1934, by Hans Andersag and coworkers at the Bayer laboratories. Chloroquine was introduced into clinical practice in 1947 for the prophylactic treatment of malaria. In the 70 years since isolation, the effects of chloroquine and hydroxychloroquine have been studied in numerous pathology beyond malaria. This has resulted in their use and, essentially repurposing, for an array of distinct diseases. This broad utility comes from discoveries regarding its pharmacology and discoveries identifying mutlitple targets underlying it mechanisms of action. It is noteworthy that the last 10 years has seen a resurgence of interest in hydroxychloroquine. Indeed, by performing a bibliographic search using hydroxychloroquine as keyword, whilst 74 papers were published in the year 2000 the number rose to 305 in 2005 and 475 in 2019.

HYDROXYCHLOROQUINE AND COVID-19

Since the start of the COVID-19 pandemic in China, hydroxychloroquine has attracted much attention. The devastating consequences of the SARs-CoV virus has led to a need to dig deep into the medicinal armamentarium to find something that works. Intensivists worldwide have explored the potential of hydroxychloroquine and several case reports and hypothesis papers have been generated that have undoubtedly led to the initiation of several clunical trials. By inserting the terms 'hydroxychloroquine and COVID-19' in PubMed the system retrieves a total of 445 papers (access 2nd June 2020). Interestingly, among these 445 papers 69 are reviews, 13 systematic reviews and 3 clinical trials. The remaining 360 are hypothesis papers and case studies. While we were writing this article a study was published in the Lancet claiming that hydroxychloroquine increased the death rate and the rate of arrhythmias followed within a matter of weeks by authors' retraction due to concerns raised on the database used. This has been followed up by the results of the RECOVERY study (https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19). In this prospective clinical trial, COVID-19 patients accessing NHS structures in the UK were enrolled. The findings from this demonstrated no benefit from hydroxychloroquine with no reduction in the risk of death among hospitalized patients. The recent move by the FDA to revoke the emergency use of hydroxychloroquine for COVID-19 has been a direct response to RECOVERY (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and).

The idea of chloroquine/hydroxychloroquine as an antiviral in not new. In 2003 Savarino and colleagues proposed the use of chloroquine as an antiviral treatment to combat modern infectious disease. Their justification for this proposal was based upon 4 characteristrics of these drugs i.e. that both inhibit i) pH-dependent steps of viral replication of several viruses including coronaviruses, ii) IL-6 and TNFα production acting as an immunosuppressor, iii) autophagy by impairing autophagosome-to-lysosome fusion; iv) p38 MAPK activation. In addition, both have been shown to function as an antitumor immune modulator that switches macrophages from M2 to tumour-killing M1 phenotype thereby decreasing immunosuppressive infiltration and enhancing antitumor T-cell immunity (see Figure 1).

This resurgence in interest in hydroxychloroquine has led to many new trials being institigated in the setting of COVID-19. Currently, in the clinicaltrial.gov database, there are 454 clinical studies on hydroxychloroquine 208 of which are in the setting of COVID-19, although the response from the MHRA to stop all recruitment to trials of these drugs has impacted upon this number (https://www.gov.uk/government/news/mhra-suspends-recruitment-to-covid-19-hydroxychloroquine-trials). These clinical trials are going to be essential if we are to understand whether there is any benefit to be

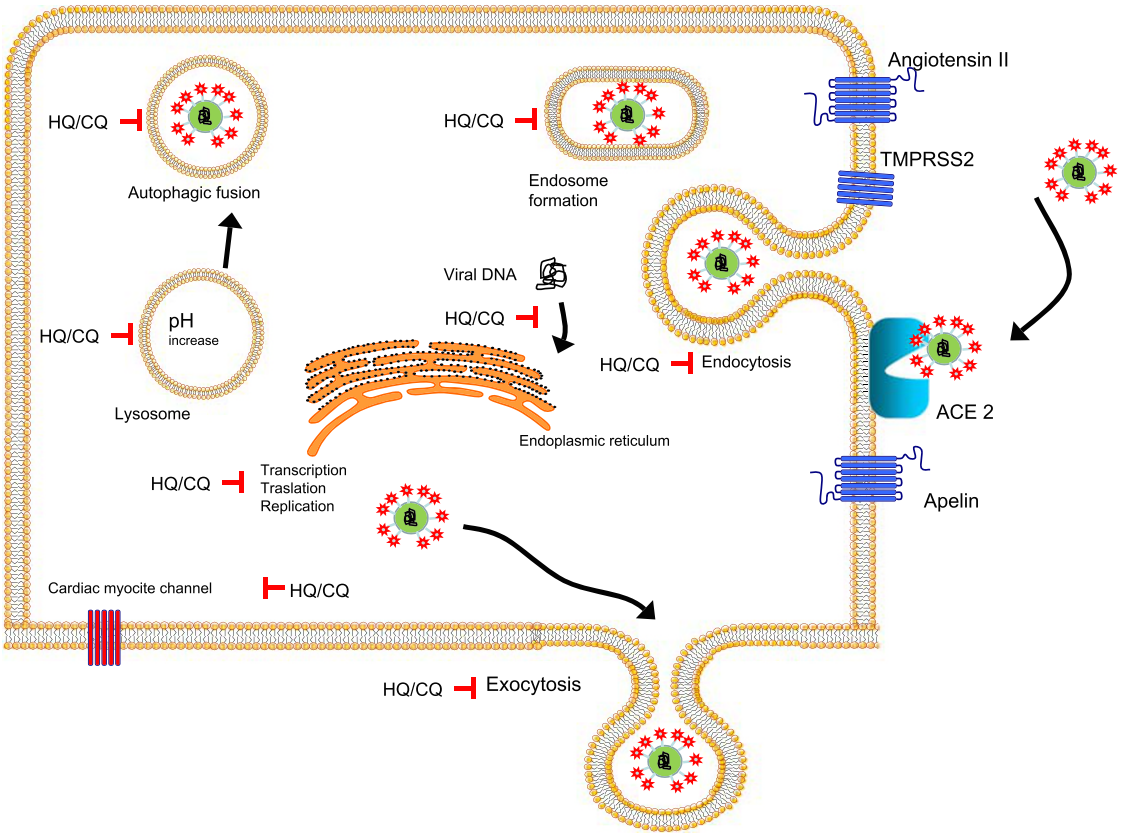

FIGURE 1 Sites of action of hydroxychloroquine and chloroquine. The symbol ⊢ denotes inhibition

had from these drugs in the clinical setting. The results of RECOVERY suggest not, however the hype surrounding these drugs is not likely to abate in the near future particularly with so many clinical trials underway. Many of the studies underway have arisen from preclinical studies that have identified novel mechanisms that have been tested in vitro and using preclinical relevant in vivo models. Studies published in BJP over 30 years are a testament to this, demonstrating that targets include transporters, receptors and channels to exert effects ranging from arrhythmia, repression of immune responses, autophagy and pulmonary vasodilatation to name a few. We would also like to highlight that one aspect of activity that has not been considered is retinal toxicity. While it is true that this side effect is present in chronic treatment such as in arthritis, the fact that it is dose-related, means caution should be taken when this drug is used for prophylactic use in patients with eye disease. We bring some of the papers published in BJP together in this timely virtual issue in a bid to help researchers understand what the risks and benefits of this drug might be in 2020.

Giuseppe Cirino[1]
Amrita Ahluwalia[2]

[1]*University of Naples Federico II, Italy*
[2]*William Harvey Research Institute, Queen Mary University of London, London, UK*

Correspondence
Amrita Ahluwalia, British Journal of Pharmacology, The Schild Plot, 16 Angel Gate, City Road, London EC1V 2PT, UK.
Email: info@bps.ac.uk